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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/780,819	02/18/2004	William A. Schumacher	HA0793 NP	3774

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EXAMINER	
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ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/780,819	SCHUMACHER ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, without traverse, with the Group II along with the species of Example 1 is acknowledged. Claims 11-17 are readable on the elected species.

Status of Application

2. By Amendment October 26, 2006, claims 1-10 have been cancelled. Claims 11-17 are currently pending for prosecution on the merits of the case.

Claim Objections

3. Claim 15 is objected to because of the following informalities: Misspelling of "a progdrug" is present. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 11-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing Factor Xia in a mammal by administration of a compound of the formula I, does not reasonably provide enablement for "inhibiting Factor XIa", "a small organic compound with an IC50..." or "a prodrug carbamate thereof". The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a method for "inhibiting Factor XIa" comprising administering a small organic compound with an IC 50 for Factor Xia of less than 120nM, 10 nM, 6 nM or 1nM (claims 11-17), namely a small organic compound of formula I (claims 15-17).

The specification defines the term "small compound" or "small molecule" as "a non-peptidic organic compound having less than 1000 molecular weight, with preferred compounds having less than 750 molecular weight, and even more preferred compounds having less than 500 molecular weight" and the term "prodrug" as "a compound which, upon administration to a subject undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I)".

The American Heritage Dictionary (Second College Edition, 1982) defines the term "inhibit" as "restrain or hold back; prevent" and "prevent" as "anticipate or counter in advance, to keep from happening". The interpretation of the instant claims allows for the complete eradication or total elimination of Factor XIa by the administration of said compounds.

With respect to the scope of enablement for "inhibiting Factor XIa",

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the preventive utility of the instant compounds.

The specification provides the effects of the claimed compounds represented by the formula, particularly Ex. No. 1-15 compounds in reducing FXIa. However, there is no demonstrated correlation that the tests and results apply to the claimed preventive utility or total elimination of Factor XIa activity embraced by the instant claims.

Since the efficacy of the claimed compound(s) in inhibiting FXIa mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to scope of enablement for "a small organic compound with an IC50..." or "a prodrug carbamate thereof',

The claims are very broad due to the vast number of possible compounds of that are described as being "a small organic compound with an IC50..." or "a prodrug carbamate thereof'. The instant claims cover plethora of "a small organic compound with an IC50... " or "a prodrug carbamate thereof" that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

The specification discloses how to make compounds of the formula I, particularly compounds of the formula (Ib). Furthermore, the specification provides assays in vitro to test said compounds (Ex. 2-15) in reducing Factor XIa activity and demonstrates that said compounds are effective in reducing thrombosis without incurring bleeding risk (Examples).

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d

1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of inhibiting Factor XIa prior to filling of the instant invention was an unpredictable art.

To practice the instant invention to the claimed scope, applicant would have to (i) make or synthesize numerous possible compounds characterized as "a small organic compound" having Factor XIa inhibiting activity or "a prodrug carbamate thereof' considering the structure-activity relationship of the compounds, (ii) screen potentially suitable compounds and (iii) assay to find out which compounds are able to "inhibits Factor XIa" at desired level (e.g., less than 120 nM, 10nM, 6nM or 1nM), and then (iv) extrapolate the test and result to the claimed therapeutic utility. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art, the skilled artisan would have not known how to extrapolate the result provided in the instant specification to the larger and highly varied genera of compounds that are characterized by "a small organic compound with an IC50..." or "a prodrug carbamate thereof', without undue amount of experimentation.

In the instant case, only limited numbers of "a small organic compound with an IC50..." and "a prodrug carbamate thereof" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The instant claims read on any compounds having "a small organic

compound with an IC50..." or "a prodrug carbamate thereof', necessitating an exhaustive search for the embodiments suitable to practice the claimed invention.

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fishcher, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575.

As discussed above, considering above factors, especially the "sufficient working examples", "the level of skill in the art", "the relative skill and the unpredictability in the pharmaceutical art", "breadth of the claims" and "the chemical nature of the invention", one having ordinary skill in the art would have to undergo an undue amount of experimentation to practice the invention commensurate in scope with these claims.

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require

appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

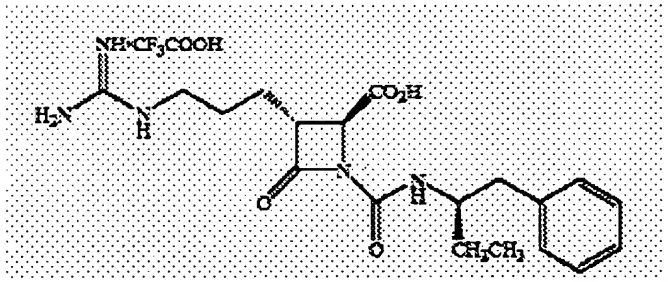
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 11-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Bisacchi et al. (US 6335324).

Bisacchi teaches the trifluoroacetate salt compound of the formula I,



, (Example 16 which is RN 253172-65-5) that is useful as a selective tryptase inhibitor that is useful as anti-inflammatory agent (abstract; Example 16; column 26, line 28 thru column 28, line 5; column 29, line 29 thru column 30, line 4).

Although Bisacchi is silent about the activity of said compound in inhibiting Factor XIa or "an IC50 for inhibiting Factor XIa " of less than 120nM, 20 nM, 10 nM, 6 nM, 3 nM or 1nM, such characteristics or properties deems to be inherent to the referenced method. The prior art directing administration of the same compound inherently possessing a therapeutic effect for the same ultimate purpose (e.g., treatment of thrombosis, stroke, myocardial infarction and etc..., see particularly column 27, lines 25-47 of the US'324) as disclosed by Applicant anticipates the claimed invention absence explicit recitation of underlying mechanism.

Conclusion

6. No Claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system,

see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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